REMARKS

The claims have been amended to compensate for the error of having listed two claims 20. Specifically, claim 19 was amended to delete claim 20, first occurrence. Claim 20, second occurrence, through claim 33 were canceled. All canceled claims were then renumbered and added as new claims. The dependencies were also appropriately changed. These amendments are not made for purposes of patentability. Thus, the scope of the claims remains unchanged.

I. Office Action Summary

A) Disposition of Claims

Claims 1-19 and 34-48 are pending in the application and are rejected.

B) Information Disclosure Statement (IDS)

The Examiner has not returned a copy of PTO form 1449 filed with the IDS dated May 25, 2004.

The Examiner is requested, respectfully, to return the form, initialed and signed, with the response to this Office Action. For the Examiner's convenience, a copy of the PTO Form 1449 filed with the Information Disclosure Statement dated May 25, 2004, is attached.

C) PTO-Form 892 - Notice of References Cited

Applicants note an error in PTO Form 892 attached to the Office Action. The Examiner listed U.S. 6,441,162 to Yasuki, et al., when it is believed that U.S. 6,441,163 to Chari, et al., was intended.

The Examiner is requested, respectfully, to correct this.

II. Detailed Action

Claim Rejections - Double Patenting

The Examiner issued a nonstatutory double patenting rejection over the claims of two of the assignee's patents (USP 6,441,163 and USP 6,436,931) and a provisional nonstatutory double patenting rejection over the claims of one of the assignee's co-pending applications (USAN 10/161,651). The Examiner asserted that the claims of the '163, '931 and '651 each make obvious the claims of the present application.

First, the undersigned notes that a nonstatutory double patenting rejection is a judicially created doctrine invented to prevent unjustified extension of a patent by allowing later patents to issue to obvious variations of the claims of earlier patents, just because the earlier application or patent is not statutory prior art to a later filed application. Therefore, the rejection is only proper where the cited patents or applications are not legally effective prior art under the provisions of 35 U.S.C. § 102/103.

Both of the cited patents and the cited '651 application appear to be legally effective prior art against the present application under 35 U.S.C. § 102(e). Therefore, the nonstatutory double patenting rejection is improper over the patents and should be removed, and the provisional nonstatutory double patenting rejection is legally improper over the cited '651 application and should be removed.

Furthermore, each of the cited patents and the cited '651 application appear to be legally effective prior art only under 35 U.S.C. § 102(e)/103. Therefore, under 35 U.S.C. § 103(c), neither the patents nor the application can be cited against the present application as long as the cited patents and application and the invention claimed in the present application were all owned by or subject to an obligation of assignment to the assignee at the time the invention claimed in the present application was made.

The assignee confirms that the requisite common ownership did exist. Therefore, none of the patents and the '651 application can be cited in an obviousness rejection.

Furthermore, even if the nonstatutory double patenting rejections were legally proper, the presently claimed invention is neither taught nor suggested by the cited references.

10/633,616 Application

The claims of the present application provide novel heterobifunctional cross-linkers that facilitate an accelerated disulfide exchange reaction rate between the modified cell binding agent and the thiol substituent on the cytotoxic drug. The heterobifunctional cross-linkers comprise, for example, a nitropyridyldithio, dinitropyridyldithio, N,N-dialkylcarboxamidopyridyldithio or di-(N,N-dialkylcarboxamido)pyridyl-dithio groups and a reactive carboxylic ester group such as a N-succinimidyl ester or a N-sulfosuccinimidyl ester group. The heterobifunctional cross-linkers of the present invention have several advantages over other cross-linkers, for example, they allow for formation of a hindered disulfide bond between the cell binding agent and the drug moiety and they provide for an accelerated disulfide exchange reaction rate with the thiol substituent on the small molecule drug.

Furthermore, as described in paragraph 21 of the specification, the cell binding agents modified with cross-linkers, such as **1**, **2**, **3a**, **3b**, **3c**, **4a**, **5a** or **5b**, exemplified in Figures 1-6, can then react with a small excess of a small molecule drug which contains a thiol moiety to give excellent yields of conjugate. Reaction rates are about 12-fold faster than with the previously described, less reactive cross-linkers. The new reagents have a further advantage in that the progress of the disulfide exchange reaction can be monitored readily because of the high extinction coefficient of the nitro-pyridine-2-thione that is released in the reaction. Lowering the

need for excess thiol has the unforeseen benefit of reducing the cleavage of internal disulfide bridges found in native proteins.

The steps of cross-linking a cell binding agent to a small molecule drug include the steps of:

(1) reacting the cell binding agent with the novel cross-linkers, such as those described by formula I or II, wherein X and Y are not both H at the same time, to yield a compound of formula III or IV in which a cell binding agent bears a cross-linker with a reactive group; and

(2) reacting the compound of formula III or IV with one or more small-molecule drugs to yield a conjugate of formula V.

Examples of some suitable cross-linkers that can be used to make the conjugate of the present invention and their synthesis are shown in FIGS. 1 to 6. Preferably, the cross-linkers are N-succinimidyl 4-(5-nitro-2-pyridyldithio)-pentanoate (**1**) or the highly water-soluble analog N-sulfosuccinimidyl 4-(5-nitro-2-pyridyldithio)-pentanoate (**2**), N-succinimidyl-4-(2-pyridyldithio) butyrate (SPDB, **3a**), N-succinimidyl-4-(5-nitro-2-pyridyldithio) butyrate (SNPB, **3b**), and N-sulfosuccinimidyl-4-(5-nitro-2-pyridyldithio) butyrate (SSNPB, **3c**), N-succinimidyl-4-methyl-4-(5-nitro-2-pyridyldithio)pentanoate (SMNP, **4a**), N-succinimidyl-4-(5-N,N-dimethylcarboxamido-2-pyridyldithio) butyrate (SCPB, **5a**) or N-sulfosuccinimidyl4(5-N.N-dimethylcarboxamido-2-pyridyldithio) butyrate (SSCPB, **5b**).

As described above, the claims of the instant application embrace a novel method of making a conjugate, and they do not use the sulfosuccinimdyl 4-(2-pyridodithio)-pentanoate cross linking agent, described by the examiner.

US 6,436,931

In contrast to the claims of the present application, the claims of the '931 patent do not teach or contemplate the use of heterobifunctional cross-linkers.

US 6,441,163

In contrast to the claims of the present application, the claims of the '163 patent are directed to a method of producing a novel maytansinoid (AB), which is essentially a complex between a maytansine (A) and a linker (B). The method of producing the novel maytansinoids claimed in the '163 patent comprises reacting the carboxyl group of N2' -deacetyl-N2 -[3-(carboxyalkyldithio)-1-oxopropyl]-maytansine with a hydroxy compound to yield a maytansinoid having a disulfide moiety that bears a reactive ester.

Furthermore, the claims of the '163 patent do not teach or contemplate the use of heterobifunctional cross-linkers.

10/161,651 Application

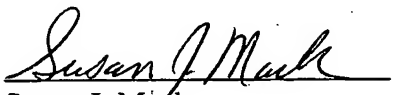
The '651 application is a divisional of the '163 patent. The claims of '651 application are directed to conjugating novel maytansinoids claimed in the parent application. The novel maytansinoids have a disulfide moiety that bears a reactive ester, which allows linkage to an appropriate cell binding agent. The presence of a reactive ester group on the maytansinoids facilitates a single step linkage to an unmodified cell binding agent. The linkers described in this application do not include heterobifunctional linkers claimed in the present application.

Thus, none of the claims of the cited references teaches or suggests the subject matter of the present application. Accordingly, the rejection, is legally improper and should be removed.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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